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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,852	02/15/2000	Jonathan L. Tilly	2653/28	5439

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KENYON & KENYON
1500 K STREET, N.W., SUITE 700
WASHINGTON, DC 20005

EXAMINER

DI NOLA BARON, LILIANA

ART UNIT PAPER NUMBER

1615

DATE MAILED: 05/24/2002

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/503,852

Applicant(s)

TILLY ET AL.

Examiner

Liliana Di Nola-Baron

Art Unit

1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 April 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23, 27-36 and 46-71 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23, 27-36 and 46-71 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

Art Unit: 1615

DETAILED ACTION

Receipt of Applicant's amendment, filed on April 10, 2002, is acknowledged.

Claim Objections

1. Claim 3 is objected to for being improperly dependent on subsequent claim 62. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim, but not to a subsequent independent claim. Appropriate correction is required.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 1-23, 27-36 and 46-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perez et al. in view of Spiegel and further in view of Igarashi et al.

The claimed invention refers to methods of protecting female reproductive system, preserving or reviving ovarian function, or ameliorating menopausal syndromes in women, comprising administering a composition comprising sphingosine-1-phosphate (SPP).

Art Unit: 1615

Perez et al. indicates that conventional cancer therapies kill normal cells and one of the most sensitive noncancerous cell type is the ovarian germ cell, and teaches that apoptosis induced by doxorubicin is blocked by sphingosine-1-phosphate (See e.g., p. 1228 and Abstract). Perez et al. teaches that exposure of women to a wide spectrum of agents that damage the ovary generally leads to irreversible sterility (See e.g., p. 1228) and the data from the study provide a strong impetus to manipulate death effector pathways in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231).

Perez et al. does not specify the method and dosage of administration of compositions comprising SPP.

Spiegel provides methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, by administration of sphingosine-1-phosphate and derivatives thereof (See e.g., col. 1, lines 9-17). Spiegel teaches that compositions containing SPP may be administered directly to the cells or parenterally to obtain concentrations of 0.1-100 μM , as well as to the epithelial tissues, such as the rectum and the vagina (See e.g., col. 1, line 46 to col. 2, line 42).

4. Igarashi et al. discloses a method of inhibiting tumor cell chemoinvasion, comprising contacting the tumor cells with an inhibitory amount of sphingosine-1-phosphate (See e.g., col. 1, line 57 to col. 2, line 48). Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate and teaches that said inhibitory amount can be determined using art-

Art Unit: 1615

recognized methods, such as dose response curves, or clinical trials, and sphingosine-1-phosphate can be administered orally, parenterally and topically, with suitable doses of sphingosine-1-phosphate depending upon the particular medical application and that the number of doses, daily dosage and course of treatment may vary from individual to individual (See e.g., col. 7, lines32-65).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Perez et al. and Spiegel to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et al. Because of the teachings of Spiegel, that sphingosine-1-phosphate is effective in treating aging diseases, and the teachings of Igarashi et al., that sphingosine-1-phosphate inhibits tumor cell chemoinvasion, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

5. Applicant's arguments filed on April 10, 2002 have been fully considered but they are not persuasive.
6. Applicant argues that none of the references alone or in combination teaches Applicant's claimed invention. Specifically, Applicant argues that Perez et al. discloses studies, which were

Art Unit: 1615

performed in vitro and does not teach protection of a female reproductive system and administration of an effective amount of the active agent, and Spiegel and Igarashi et al. do not teach anything about the female reproductive system. Additionally, Applicant argues that there is no motivation to combine the references. In response to said arguments, it is noted that Perez et al. teaches that exposure of women to a wide spectrum of agents that damage the ovary generally leads to irreversible sterility (See e.g., p. 1228) and the data from the study provide a strong impetus to manipulate death effector pathways in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231). Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases, including aging, which is defined by Applicant as a natural insult (See Applicant's specification, p. 15). Additionally, Spiegel teaches that SPP may be administered to the epithelial tissues, such as the rectum and the vagina (See e.g., Col. 1, line 46 to col. 2, line 26). Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate and teaches that said inhibitory amount can be determined using art-recognized methods, such as dose response curves, or clinical trials, and sphingosine-1-phosphate can be administered orally, parenterally and topically (See e.g., col. 7, lines 32-65). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al. and Spiegel to devise methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et

Art Unit: 1615

al. The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

7. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Perez et al. contemplates methods of treatment of the female reproductive system using sphingosine-1-phosphate in vivo based on studies, which were performed in vitro, Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases, including aging, and Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al. and Spiegel to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et al. The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

Art Unit: 1615

Conclusion

8. Claims 1-23, 27-36 and 46-71 are rejected.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Application/Control Number: 09/503,852

Page 8

Art Unit: 1615

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

May 23, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600